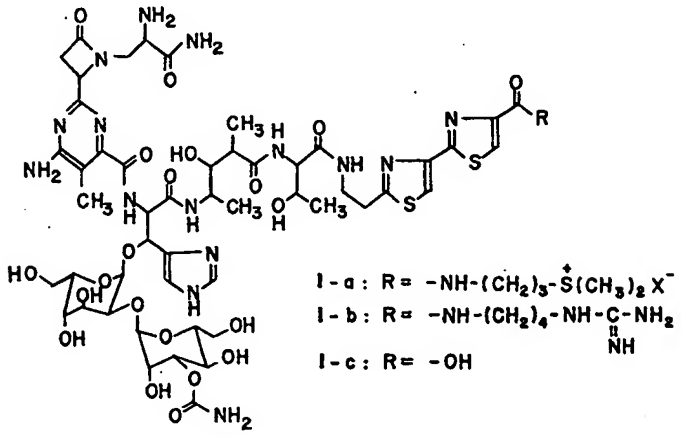
CHEMICAL CLEAVAGE OF BLEOMYCIN TO BLEOMYCINIC ACID AND SYNTHESIS OF NEW BLEOMYCINS

Sir:

Bleomycins are a group of related glycopeptide antitumor antibiotics, the structure of which was recently elucidated by chemical and spectroscopic methods.[1] The bleomycins (I, R=an amine) differ in the terminal amine and show varying biological activity.



I-a: R= $-NH-(CH_2)_3-\overset{+}{S}(CH_3)_2\ X^-$

I-b: R= $-NH-(CH_2)_4-NH-\overset{\overset{NH}{\|}}{C}-NH_2$

I-c: R= $-OH$

New bleomycins have been produced by biosynthesis. Specific amines are added to the fermentation and are incorporated in the terminal amine moiety.[2] Bleomycin B_2 (I-b) is hydrolyzed into bleomycinic acid (I-c) and agmatine by an enzyme isolated from *Fusarium anguioides*.[3] Bleomycinic acid can be coupled with specific amines by use of a water-soluble carbodiimide to form new semi-synthetic bleomycins.

In this communication we are reporting the selective chemical cleavage of bleomycin A_2 (I-a) to bleomycinic acid and the preparation of new semisynthetic bleomycins form an intermediate ester by aminolysis.

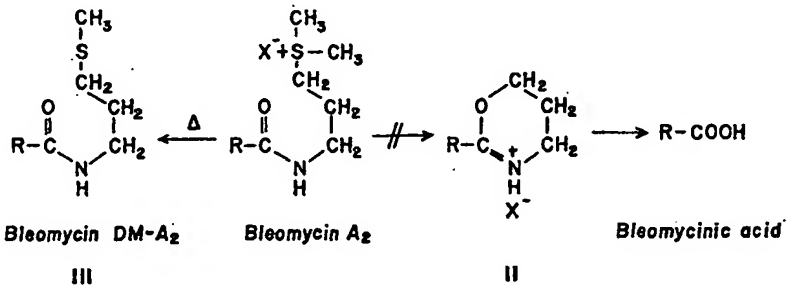
From the structure of bleomycins it is obvious that there are many functional groups which can easily be hydrolyzed. Our aim is to hydrolyze selectively the terminal peptide bond which is one of the most stable in the molecule. We chose bleomycin A_2 as the starting material because it is a main component of natural bleomycins and has a reactive sulfonium group in the amine moiety.

We were not successful in obtaining appreciable amounts of bleomycinic acid directly from bleomycin A_2 *via* the cyclic imino ether (**II**). However, we found that one of the methyl groups of the dimethyl sulfonium group was easily eliminated by pyrolysis without any change in the rest of the molecule. The yield of bleomycin demethyl-A_2 (DM-A_2) (**III**) from bleomycin A_2 was more than 70 % under reduced pressure at 100°C for 24 hours.

We thought that if a cyano group could be introduced in place of the methyl group which was removed by pyrolysis, methyl thiocyanate, a better leaving group than dimethyl sulfide, would be eliminated smoothly accompanied by formation of the cyclic imino ether, **II**.

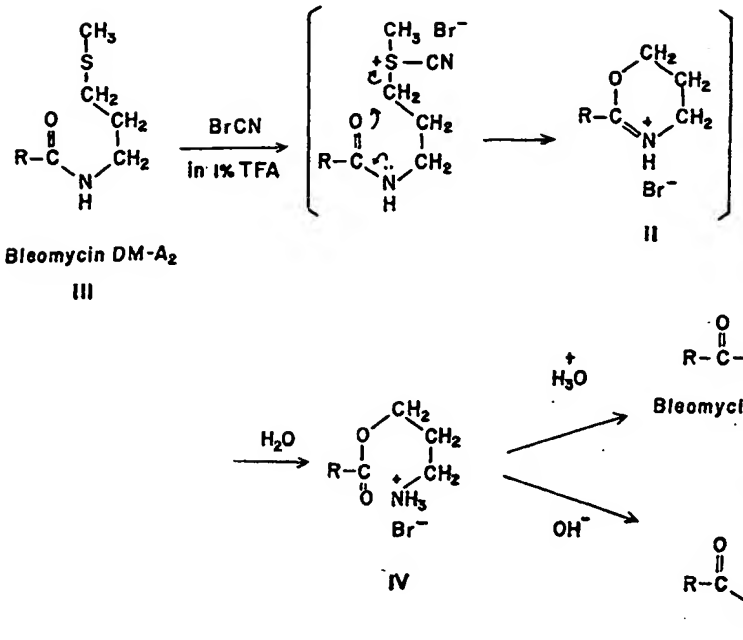
Bleomycin DM-A_2 was dissolved in 1 % trifluoroacetic acid and reacted with excess cyanogen bromide at 27°C for 18 hours. The product was separated by CM-Sephadex C-25 column chromatography, and bleomycinic acid 3-aminopropyl ester (**IV**) was obtained in 75 % yield.

Under alkaline conditions, the ester carbonyl of **IV** shifted easily to the terminal amino group to form the stable amide (**V**). By mild acid



Bleomycin DM-A_2 Bleomycin A_2 Bleomycinic acid

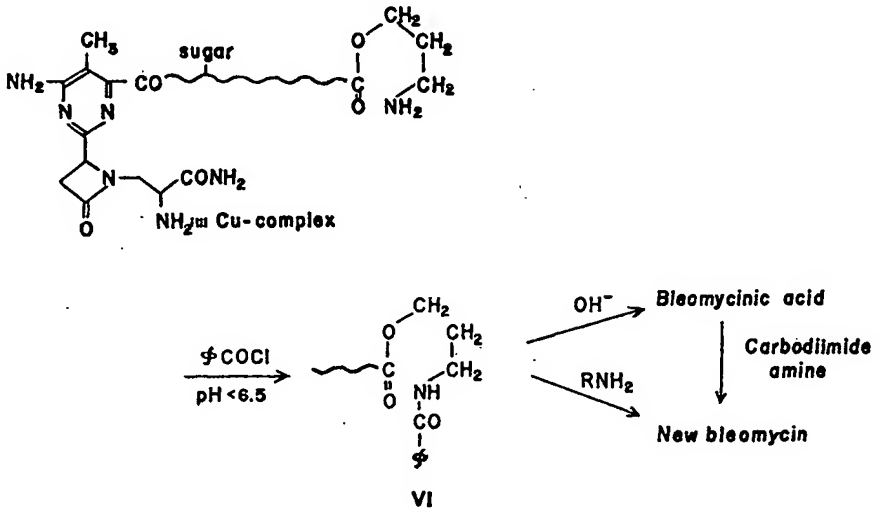
III II



hydrolysis of IV, bleomycinic acid was obtained in about 50 % yield.

To block the acyl migration in alkali, selective acylation of the terminal amino group of VI was studied. The primary amino group present in the bleomycinic acid moiety was protected by copper-chelation and N-benzoylation was carried out with benzoyl chloride at pH 6.5. The desired mono-*N*-benzoyl IV (VI) was obtained in almost quantitative yield. Mild alkaline hydrolysis (0.025 N KOH at 0°C) of VI afforded bleomycinic acid in over 90 % yield. Thus, selective chemical cleavage of bleomycin A_2 to form bleomycinic acid was achieved.

New semi-synthetic bleomycins were also prepared as follows: compound VI was treated with a specific amine in methanol solution at room temperature. The specific amine was incorporated as the terminal amine moiety to form a new semi-synthetic bleomycin in over 80 % yield. Thus, direct transformation from compound VI to new semi-synthetic bleomycins was achieved.



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